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(54) Title: METHOD OF TREATMENT AND PHARMACEUTICAL COMPOSITION

(57) Abstract

The invention relates to a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, hypertension in patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke, comprising administering a therapeutically effective amount of combination of (i) the AT₁-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a Calcium channel blocker or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment and to corresponding pharmaceutical combination composition.

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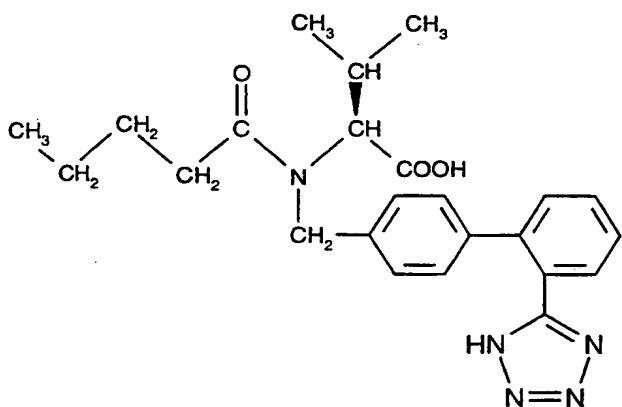
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Method of Treatment and Pharmaceutical Composition

The present invention relates to a pharmaceutical composition comprising as active ingredients

(i) the AT₁ receptor antagonist (S)-N-(1-carboxy-2-methyl-prop-1-yl)-N-pentanoyl-N-[2'(1H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine (valsartan) of formula (I)



or a pharmaceutically acceptable salt thereof and

(ii) a Calcium channel blocker (CCB) or a pharmaceutically acceptable salt thereof and
 (iii) a pharmaceutically acceptable carrier.

Valsartan is specifically and generically disclosed in EP 0443983 A.

The class of CCBs essentially comprises dihydropyridines (DHPs) and non-DHPs such as diltiazem-type and verapamil-type CCBs.

A CCB useful in said combination is preferably a DHP representative selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, nulgidipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, and in each case, a pharmaceutically acceptable salt thereof. All these CCBs are therapeutically used, e.g. as anti-hypertensive, anti-angina pectoris or anti-arrhythmic drugs. Preferred CCBs comprise amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and verapamil, or, e.g. dependent on the specific CCB, a pharmaceutically acceptable salt thereof. Especially preferred as DHP is

amlodipine or a pharmaceutically acceptable salt, especially the besylate, thereof. An especially preferred representative of non-DHPs is verapamil or a pharmaceutically acceptable salt, especially the hydrochloride, thereof.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic centre, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic centre. The compounds having at least one acid group (for example COOH) can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound of formula comprises e.g. both a carboxy and an amino group.

Preferred salts of corresponding CCBs are amlodipine besylate, diltiazem hydrochloride, fendiline hydrochloride, flunarizine di-hydrochloride, gallopamil hydrochloride, mibefradil di-hydrochloride, nicardipine hydrochloride, and verapamil hydrochloride.

The vasoconstrictive effects of angiotensin II are produced by its action on the non-striated smooth muscle cells, the stimulation of the formation of the adrenergic hormones epinephrine and norepinephrine as well as the increase of the activity of the sympathetic nervous system as a result of the formation of norepinephrine. Angiotensin II also has an influence on the electrolytic balance, produces e.g. antinatriuretic and antidiuretic effects in the kidney and thereby promotes the release of, on the one hand, the vasopressin peptide from the pituitary gland and, on the other hand, of aldosterone from the adrenal glomerulosa. All these influences play an important part in the regulation of blood pressure, in increasing both circulating volume and peripheral resistance. Angiotensin II is also involved in cell growth and migration and in extracellular matrix formation.

Angiotensin II interacts with specific receptors on the surface of the target cell. It has been possible to identify receptor subtypes which are termed e.g. AT₁- and AT₂-receptors. In recent times great efforts have been made to identify substances that bind to the AT₁-receptor. Such active ingredients are often termed angiotensin II antagonists. Because of the inhibition of the AT₁-receptor such antagonists can be used e.g. as antihypertensives or for the treatment of congestive heart failure.

Angiotensin II antagonists are therefore understood to be those active ingredients which bind to the AT₁-receptor subtype but do not result in activation of the receptor.

Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of antihypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different mode of action does not necessarily lead to combinations with advantageous effects.

AT₁ antagonist and CCB reduce intracellular calcium by different and complementary mechanisms and facilitate the vasodilator effects of nitric oxide, being particularly effective in reversing endothelium dysfunction.

All the more surprising is the experimental finding that the combined administration of the AT₁-antagonist valsartan or a pharmaceutically acceptable salt thereof and a CCB or a pharmaceutically acceptable salt thereof results not only in a synergistic therapeutic effect but also in additional benefits resulting from combined treatment such as a surprising prolongation of efficacy and a broader variety of therapeutic treatment. This includes hemodynamic, renal, antiproliferative, antithrombotic and antiatherogenic properties.

The measurement of cardiac mass to assess treatment-induced regression of hypertrophy provided data to support a supra-additive effect of combination of the present invention. Left ventricular hypertrophy is an independent risk factor for the development of myocardial infarction. Thus, effective blood pressure lowering coupled with the ability to regress or prevent the development of left ventricular hypertrophy has an impact on two important and contributing factors for heart failure.

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

It can be shown that combination therapy with valsartan and a calcium channel blocker results in a more effective antihypertensive therapy (whether for malignant, essential, renovascular, diabetic, isolated systolic, or other secondary type of hypertension) through improved efficacy as well as a greater responder rate. The combination is also useful in the treatment or prevention of (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter. It can further be shown that a valsartan + CCB therapy proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A valsartan plus CCB combination is also useful in treating atherosclerosis, angina (whether stable or unstable), and renal insufficiency (diabetic and non-diabetic). Furthermore, combination therapy using valsartan and a CCB can improve endothelial dysfunction, thereby providing benefit in diseases in which normal endothelial function is disrupted such as heart failure, angina pectoris and diabetes, e.g. non-insulin dependent diabetes mellitus (NIDDM). Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke.

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the hereinbefore and hereinafter indicated therapeutic indications.

Representative studies are carried out with a combination of valsartan and amlodipine, e.g. applying following methodology. All experiments are performed in spontaneously hypertensive rats (SHR) supplied by Taconic Farms, Germantown, New York (Tac:N(SHR)fBR). A radiotelemetric device (Data Sciences International, Inc., St. Paul, Minnesota) is implanted into the lower abdominal aorta of all test animals between the ages of 14 to 16 weeks of age. All SHR are allowed to recover from the surgical implantation procedure for at least 2 weeks prior to the initiation of the experiments. The radiotransmitter is fastened ventrally to the musculature of the inner abdominal wall with a silk suture to prevent movement. Cardiovascular parameters are continuously monitored via the radiotransmitter and transmitted to a receiver where the digitized signal is then collected

and stored using a computerized data acquisition system. Blood pressure (mean arterial, systolic and diastolic pressure) and heart rate are monitored in conscious, freely moving and undisturbed SHR in their home cages. The arterial blood pressure and heart rate are measured every 10 minutes for 10 seconds and recorded. Data reported for each rat represent the mean values averaged over a 24 hour period and are made up of the 144 time points of 10 minute duration samples collected each day. The baseline values for blood pressure and heart rate consist of the average of three consecutive 24 hour readings taken prior to initiating the drug treatments. All rats are individually housed in a temperature and humidity controlled room and are maintained on a 12 hour light/dark cycle.

In addition to the cardiovascular parameters, weekly determinations of body weight also are recorded in all rats. Since all treatments are administered in the drinking water, water consumption is measured five times per week. Valsartan and amlodipine doses for individual rats are then calculated based on water consumption for each rat, the concentration of drug substance in the drinking water, and individual body weights. All drug solutions in the drinking water are made up fresh every three to four days.

Upon completion of the 6 week treatment, SHR are anesthetized and the heart rapidly removed. After separation and removal of the atrial appendages, left ventricle and left plus right ventricle (total) are weighed and recorded. Left ventricular and total ventricular mass are then normalized to body weight and reported. All values reported for blood pressure and cardiac mass represent the group mean + sem.

Valsartan and amlodipine are administered via the drinking water either alone or in combination to SHR beginning at 18 weeks of age and continued for 6 weeks. Based on a factorial design, seven (7) treatment groups are used to evaluate the effects of combination therapy on blood pressure and heart rate. Treatment groups consist of valsartan alone in drinking water at a concentration of 240 mg/liter (high dose), amlodipine alone at a concentration of 120 mg/liter (high dose), valsartan (120 mg/liter) + amlodipine (60), valsartan (120) + amlodipine (120), valsartan (240) + amlodipine (60), valsartan (240) + amlodipine (120) and a vehicle control group on regular drinking water. Thus, 4 groups of SHR receive combination therapy.

Studies have been performed in SHR and demonstrate that the addition of a CCB confers additional benefit over that of valsartan monotherapy. The Area Under the Curve (AUC) for blood pressure reflects the changes in response to 6 week treatment in conscious SHR.

Upon completion of the 6 week treatment period, hearts are removed for assessment of left ventricle mass and normalized to body weight.

The available results indicate an unexpected beneficial effect of a combination according to the invention.

Further representative studies are carried out with a combination of valsartan and an CCB, especially a non-DHP representative thereof, such as verapamil.

Diabetic renal disease is the leading cause of end-stage renal diseases. Hypertension is a major determinant of the rate of progression of diabetic diseases, especially diabetic nephropathy. It is known that a reduction of blood pressure may slow the reduction of diabetic nephropathy and proteinuria in diabetic patients, however dependent on the kind of antihypertensive administered.

In diabetic SHRs the presence of hypertension is an important determinant of renal injury, manifesting in functional changes such as albuminuria and in ultrastructural injury. For example, diabetic SHRs show ventricular hypertrophy and develop nephropathy resulting in sudden death events. Accordingly, the use of this animal model is well-applied in the art and suitable for evaluating effects of drugs on the development of diabetic renal diseases. There is a strong need to achieve a significant increase of the survival rate by treatment of hypertension in diabetes especially in NIDDM. It is known that CCBs are not considered as first line antihypertensives e.g. in NIDDM treatment. Though some kind of reduction of blood pressure may be achieved with CCBs, they may not be indicated for the treatment of renal disorders associated with diabetes. Surprisingly, treatment of diabetes associated with hypertension with the combination of valsartan and a CCB, especially a non-DHP, preferably verapamil, proved to result in the considerable reduction of sudden death events and consequently in a significant degree of increase of the survival rate in the experimental model using diabetic SHRs.

Diabetes is induced in SHRs aged about 6 to 8 weeks weighing about 250 to 300 g by treatment e.g. with streptozotocin. The drugs are administered by twice daily gavage. Untreated diabetic SHRs are used as control group (group 1). Other groups of diabetic SHRs are treated with 30 mg/kg of valsartan (group 2), with 20 mg/kg of verapamil (group 3) and with a combination of 20 mg/kg of valsartan and 15 mg/kg of verapamil (group 4).

On a regular basis, besides other parameters the survival rate after 21 weeks of treatment is being monitored. In week 21 of the study, following survival rates have been determined:

Test Group	Survival Rate [%]
1	29.7
2	45.9
3	42.9
4	67.1

The results of this study clearly show, that though CCBs are not normally used for the treatment of hypertension in diabetic patients, not only the blood pressure is reduced but moreover the survival rate is drastically increased when administering to diabetic SHRs a combination of valsartan and verapamil (the amounts of both components in the combination being reduced versus the amounts of the single drugs when administered alone). The increased survival seen in diabetic SHR is consistent with an attenuation of end-organ damage. Accordingly, the combination of valsartan and a CCB may be used for the treatment (and also for the prevention) of diabetes, e.g. of hypertension in diabetic patients, especially in hypertensive patients with NIDDM, and may be used for slowing the progression of diabetic renal diseases, such as diabetic nephropathy associated with NIDDM, and for reducing proteinuria in diabetic patients.

It is the object of this invention to provide a pharmaceutical combination composition, e.g. for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, e.g. hypertension in diabetic patients, especially in hypertensive patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke which composition comprises (i) the AT₁-antagonists valsartan or a

pharmaceutically acceptable salt thereof and (ii) a CCB or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In this composition, components (i) and (ii) can be obtained and administered together, one after the other or separately in one combined unit dose form or in two separate unit dose forms. The unit dose form may also be a fixed combination.

A further aspect of the present invention is the use of a pharmaceutical composition comprising (i) the AT₁-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a CCB or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier for the manufacture of a therapeutically effective pharmaceutical composition for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae, supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, stable angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, e.g. hypertension in diabetic patients, especially in hypertensive patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke.

A further aspect of the present invention is a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae, supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, e.g. hypertension in diabetic patients, especially in hypertensive patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular

disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke, comprising administering a therapeutically effective amount of combination of (i) the AT₁-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a CCB or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

A therapeutically effective amount of each of the components of the combination of the present invention may be administered simultaneously or sequentially and in any order.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application.

The novel pharmaceutical preparations contain, for example, from about 10 % to about 100 %, preferably 80%, preferably from about 20 % to about 60 %, of the active ingredient.

Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

The determination of the dose of the active ingredients necessary to achieve the desired therapeutic effect is within the skill of those who practice in the art. The dose depends on the warm-blooded animal species, the age and the individual condition and on the manner of administration. In the normal case, an approximate daily dose in the case of oral administration for a patient weighing approximately 75 kg for oral application is of about 10 mg to about 200 mg, especially about 20 to about 120 mg, most preferably about 40 mg to

about 80 mg for valsartan and about 1.0 mg to about 180 mg, preferably about 2.5 mg to about 50 mg, for the CCB, depending on the specific CCB.

The following example illustrates the invention described above; however, it is not intended to limit its extent in any manner.

Valsartan Tablet Formulation 80 mg + Amlodipine 5 mg (Rollercompaction)

Dosage (mg)	80 mg Valsartan + 5 mg Amlodipine
Diameter (mm)	9
Shape	round
Breaking line	without
Tablet-weight (mg)	215

Formulation of the Tablet Valsartan 80 mg + Amlodipine 5 mg

	Dosage Strength	Function of the Excipient in the Formulation	80 mg Valsartan + 5 mg Amlodipine
I.	Compactate		mg:
1.	Valsartan DS	drug substance	80.0
2.	Amlodipine DS	drug substance	5.0
3.	Avicel PH 102	filler	104.0
4.	PVPP-XL	disintegrant	20.0
5.	Aerosil 200	glidant	0.75
6.	Magnesium-stearate	lubricant	2.5
II.	Outer Phase		
7.	Aerosil 200	glidant	0.75
8.	Magnesium-stearate	lubricant	2.0
	total		215.0

What is claimed is:

1. Use of a combination of (i) the AT₁-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a Calcium channel blocker or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae, supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, hypertension in diabetic patients, hypertension in patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, Alzheimer's, and stroke.
2. Use as claimed in claim 1, wherein a Calcium channel blocker is a DHP representative selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, nulgildipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, or is a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibepradil, anipamil, tiapamil and verapamil, and in each case, a pharmaceutically acceptable salt thereof is used as component (ii).
3. Use as claimed in claim 1, wherein amlodipine or verapamil, or, in each case, a pharmaceutically acceptable salt thereof is used as component (ii).
4. A pharmaceutical combination composition comprising (i) the AT₁-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a Calcium channel blocker or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.
5. A pharmaceutical combination composition as claimed in claim 4 for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic

cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, hypertension in patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction, Alzheimer's, and stroke.

6. A pharmaceutical combination composition as claimed in claim 4, comprising as Calcium channel blocker a DHP representative selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, or a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibepradil, anipamil, tiapamil and verapamil, or in each case, a pharmaceutically acceptable salt thereof.
7. A pharmaceutical combination composition as claimed in claim 4, comprising amlodipine or a pharmaceutically acceptable salt thereof.
8. A pharmaceutical combination composition as claimed in claim 4, comprising verapamil or a pharmaceutically acceptable salt thereof.
9. A pharmaceutical combination composition as claimed in claim 4 for oral application, comprising of about 10 mg to about 200 mg of valsartan.
10. A pharmaceutical combination composition as claimed in claim 4 for oral application, comprising about 1.0 mg to about 180 mg of a Calcium channel blocker.



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(54) Title: ANTIHYPERSENSITIVE COMBINATION OF VALSARTAN AND CALCIUM CHANNEL BLOCKER			
(57) Abstract <p>The invention relates to a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, hypertension in patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke, comprising administering a therapeutically effective amount of combination of (i) the AT₁-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a Calcium channel blocker or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment and to corresponding pharmaceutical combination composition.</p>			

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INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 99/04842

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/41 A61K31/44 A61K31/275

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>MCINNES G. T.: "Clinical advantages of valsartan" <i>CARDIOLOGY</i>, vol. 91, no. suppl., August 1999 (1999-08), pages 14-18, XP000866179 abstract page 16, column 2</p> <p>---</p> <p style="text-align: center;">-/--</p>	1-6, 9, 10

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

21 January 2000

14.04.00

Name and mailing address of the ISA

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Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04842

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>COREA L. ET AL: "Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: A comparative study of the efficacy and safety against amlodipine" <i>CLINICAL PHARMACOLOGY & THERAPEUTICS</i>, vol. 60, no. 3, September 1996 (1996-09), pages 341-346, XP000866180 abstract page 342, column 2, paragraph 2; tables 2,3</p> <p style="text-align: center;">---</p>	1-7,9,10
X,P	<p>BAKRIS G. L. ET AL: "Clinical efficacy and safety profiles of AT I receptor antagonists" <i>CARDIOVASCULAR REVIEWS & REPORTS</i>, vol. 20, no. 2, February 1999 (1999-02), pages 77-100, XP000866263 page 90; table 3 page 94; table 4</p> <p style="text-align: center;">---</p>	1-10
X	<p><i>CHEMICAL ABSTRACTS</i>, vol. 17, no. 124, 22 April 1996 (1996-04-22) Columbus, Ohio, US; abstract no. 220073,</p> <p>FUJIMURA Y ET AL: "Antihypertensive effect of a combination of valsartan and hydrochlorothiazide, nifedipine or propranolol in spontaneously hypertensive rats" XP002051904 abstract</p> <p>& FUJIMURA Y. ET AL: <i>YAKURI TO CHIRYO</i>, vol. 23, no. 12, - 1995 pages 3241-3247,</p> <p style="text-align: center;">-----</p>	1-6,9,10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/04842

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

7 complete, 1-6,9,10 partially

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 99/04842

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,4,5,9,10

Present claims 1,4,5,9,10. relate to a composition defined by reference to the following parameter: a calcium channel blocker. The use of this parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameter the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search not fully possible. Moreover the claims cover all compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is not fully possible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely the search has been restricted to the compounds mentioned in the description and in claims 2,3,6-8.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 99/04842

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 7 complete, 1-6,9,10 partially

Antihypertensive combination of valsartan and a dihydropyridine calcium channel blocker (amlodipine preferred)

2. Claims: 8 complete, 1-6,9,10 partially

Antihypertensive combination of valsartan and non dihydropyridine calcium channel blocker (verapamil preferred)

